Effects of isoflurane–nitrous oxide anaesthesia on insulin secretion in female patients

J. P. DESBOROUGH, M. G. KNOWLES AND G. M. HALL

Summary

In vitro studies suggest that volatile anaesthetic agents may directly inhibit insulin secretion. It is unclear if supplementation of anaesthesia with isoflurane impairs insulin secretion. We performed a 5-g i.v. glucose tolerance test in 21 patients before and during anaesthesia which was maintained with either 1 or 2 MAC of isoflurane in nitrous oxide, or no volatile agent. The study was carried out before surgery to avoid the influence of hormonal responses to trauma. A significant glycaemic response occurred during both i.v. glucose tolerance tests in all three groups of patients. Serum insulin concentrations were measured and the acute increase in insulin concentration at 3 min and area under the curve for 15 min were calculated. Both variables decreased significantly in all three groups during the tests performed under anaesthesia compared with tests carried out before anaesthesia.

Methods and results

Surgical trauma results in a hormonal and metabolic response, which includes an increase in the concentrations of catabolic hormones and hyperglycaemia. In vitro experiments showed a significant inhibitory effect of volatile anaesthetic agents on insulin secretion from rat pancreatic islets. Direct impairment of insulin release in humans by these agents may augment the glycaemic response to catabolic hormone secretion found in the perioperative period.

There are few clinical studies on the effects of inhalation anaesthesia on insulin secretion. Therefore, we have studied the insulin response to a 5-g i.v. glucose tolerance test (ivgtt) in healthy patients, both awake and during anaesthesia with 1 or 2 MAC of isoflurane in nitrous oxide, or an anaesthetic without a volatile agent, to determine if there was a specific inhibitory effect of isoflurane on insulin secretion.

Methods and results

The study was approved by the local Hospital Research Ethics Committee. Patients were undergoing elective tubal surgery for infertility. Any subject known to have polycystic ovarian disease, or metabolic or endocrine disorder, or receiving drugs known to alter hormone secretion and metabolism was excluded. All patients gave written, informed consent to the study.

Patients fasted overnight and the studies started in the morning. Premedication with morphine 10 mg and hyoscine 0.4 mg i.m. was given immediately before transfer from the ward.

Two control blood samples were obtained from a central venous catheter and, after 5 min, 50% glucose 10 ml was given i.v. as a bolus into the contralateral arm. Blood samples were obtained after 3, 4, 5, 7, 10 and 15 min. At the end of the awake ivgtt, after the 15-min sample, the patient rested until 60 min.

On completion of the first ivgtt, sealed envelopes were used to allocate patients randomly to receive 0, 1 or 2 MAC of isoflurane in 70% nitrous oxide after induction of anaesthesia. Fentanyl 2 μg kg⁻¹ i.v. was given and anaesthesia was induced with thiopental.

The trachea was intubated after vecuronium 0.1 mg kg⁻¹ and the lungs were ventilated with 70% nitrous oxide in oxygen and isoflurane, as determined by study allocation. Continuous monitoring of partial pressure of expired carbon dioxide and of inspired and expired isoflurane was undertaken and expired carbon dioxide maintained at 4.5–5.0 kPa. In those patients allocated to receive 1 or 2 MAC of isoflurane, the designated partial pressure was achieved rapidly by adjusting the inspired isoflurane concentration (5–10 min after intubation).

Blood samples were collected immediately after induction of anaesthesia and intubation, and 10 min after steady end-tidal isoflurane values at the required MAC were achieved. A similar interval was allowed in patients allocated to the 0 MAC group before collection of another sample. The ivgtt was then repeated during anaesthesia and blood samples collected after 3, 4, 5, 7, 10 and 15 min. Supplements were made to the anaesthetic, where appropriate, and surgery started.

Samples were analysed for blood glucose, serum insulin and cortisol, and plasma catecholamines concentrations, as described previously. For each patient, the insulin response to each ivgtt was calculated as the area under the curve (AUC) from 0 min to the 15 min sample by the trapezium method. The acute insulin response (AIR) was calculated as the absolute increase in insulin concentration from the
**Isoflurane and insulin secretion**

Table 1  
Acute insulin response (AIR) and insulin response (AUC) 0–15 min, in each patient. Between-group differences in AIR: awake P=0.54, anaesthetized P=0.26. Between-group differences in AUC: awake P=0.31, anaesthetized P=0.05

<table>
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<tr>
<th>Patient No.</th>
<th>0 MAC</th>
<th>Awake</th>
<th>Anaes.</th>
<th>1 MAC</th>
<th>Awake</th>
<th>Anaes.</th>
<th>2 MAC</th>
<th>Awake</th>
<th>Anaes.</th>
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<td>Acute insulin response (AIR) (μl litre⁻¹ min⁻¹)</td>
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<td>Median (range)</td>
<td>44.4 (18.0–110.9)</td>
<td>P&lt;0.05</td>
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<td>P&lt;0.05</td>
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<td>Insulin response (AUC) 0–15 min (μl litre⁻¹ min⁻²)</td>
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<tr>
<td>Median (range)</td>
<td>412 (78–564)</td>
<td>P&lt;0.05</td>
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<td>P&lt;0.05</td>
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baseline sample immediately preceding each ivgtt to the value of the 3-min sample.³

Differences in blood glucose values within each group with respect to the baseline sample of each ivgtt were analysed by two-way analysis of variance with Dunnet’s test. Differences between the three groups were estimated by one-way analysis of variance. For insulin data, statistical analysis of differences in the calculated AIR and AUC between the three groups, awake and asleep, was by the Kruskal–Wallis test. Within each group, differences between the two ivgtts were analysed by Wilcoxon matched pairs signed rank sum test. P<0.05 was taken to be statistically significant.

We studied 27 patients. At operation, six patients were found to have ovaries with a polycystic appearance and were excluded from analysis. The results from seven patients were evaluated in each group. Median age was 31 (range 26–36), 32 (29–38) and 29 (24–39) yr for the 0, 1 and 2 MAC groups, respectively. Mean weight was 62.2 (SD 3.2), 59.4 (5.9) and 56.7 (7.4) kg, respectively, for the 0, 1 and 2 MAC groups. No patients reported any event which suggested awareness during the study.

In the awake ivgtt, blood glucose increased significantly in all three groups at 3 min by at least 2.6 mmol litre⁻¹ (P<0.05). There was no significant difference in glucose values between the three groups of patients. A similar glycaemic response was seen in the ivgtt during anaesthesia, but the increase was significantly greater in the 2 MAC group at 3 min (F=7.34, P=0.008). At 15 min, blood glucose concentration was greater in the 1 and 2 MAC groups than in the 0 MAC group (F=6.57, P=0.012).

Both AIR and AUC decreased significantly in all three groups during anaesthesia. However, there was no difference between the groups, either awake or anaesthetized, in AIR or AUC (table 1).

There were no significant differences in circulating norepinephrine, epinephrine or cortisol concentrations between the three groups.

Mean arterial pressure (MAP) did not change significantly in any group during the awake ivgtt. It decreased in all groups after induction of anaesthesia, although this was significant only in the 1 and 2 MAC groups (P<0.05). Changes in heart rate during the study mirrored those of MAP.

**Comment**

We have found that after induction of anaesthesia, the insulin response to a 5-g ivgtt decreased significantly compared with the same test performed awake. The only relevant previous clinical study of isoflurane used a large dose of glucose (0.33 mg kg⁻¹ i.v.) that resulted in circulating glucose values of up to 20 mmol litre⁻¹.¹ More importantly, the investigators did not examine the effects of anaesthesia without volatile supplementation.

The influence on insulin secretion of the other drugs used in this study (morphine, hyoscine, fentanyl, thiopental and nitrous oxide) cannot be excluded. However, these agents were common to all three groups and indicate that short-term exposure to isoflurane in a clinical setting does not further decrease insulin release. A group size of nine was chosen for the clinical studies as this sample size was adequate to decrease insulin secretion two-fold in vitro. However, six patients were excluded, and therefore the power of the study was reduced to 45% with a standardized difference of 1.0.

Cardiovascular depression after induction of anaesthesia may lead to a decrease in splanchnic blood flow with a consequent decrease in insulin reaching the peripheral circulation. Isoflurane anaesthesia results in vasodilatation of the splanchnic bed in humans and an increase in blood flow. In dogs, mechanical reduction of pancreatic blood flow was not associated with a proportionate decrease in insulin release.⁶ Thus isoflurane is unlikely to have a major inhibitory effect on insulin release mediated by alterations in splanchnic blood flow.
Acknowledgement

Financial support for assays performed in this study was received from the Association of Anaesthetists of Great Britain and Ireland. Full data are available from the authors.

References